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Staudinger/aza-Wittig reaction to access N^{β}-protected amino alkyl isothiocyanates†

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A unified approach to access N^{β}-protected amino alkyl isothiocyanates using N^{β}-protected amino alkyl azides through a general strategy of Staudinger/aza-Wittig reaction is described. The type of protocol used to access isothiocyanates depends on the availability of precursors and also, especially in the amino acid chemistry, on the behavior of other labile groups towards the reagents used in the protocols; fortunately, we were not concerned about both these factors as precursor-azides were prepared easily by standard protocols, and the present protocol can pave the way for accessing title compounds without affecting Boc, Cbz and Fmoc protecting groups, and benzyl and tertiary butyl groups in the side chains. The present strategy eliminates the need for the use of amines to obtain title compounds and thus, this method is step-economical; additional advantages include retention of chirality, convenient handling and easy purification. A few hitherto unreported compounds were also prepared, and all final compounds were completely characterized by IR, mass, optical rotation, and ^{1}H and ^{13}C NMR studies.

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Introduction

Isothiocyanates are an important class of compounds and a focus of interest in contemporary organic chemistry owing to their wide range of biological activities[1] and uses as potential precursors for accessing thioamides,[2] thioureas[3] and various heterocyclic compounds.[4] On the application part, based on structural desirabilities of the final compounds, various isothiocyanates having different skeletal structures are used.

Isothiocyanates are most commonly synthesized from amines, isonitriles and azides (Fig. 1). Thiophosgene upon thiocarbonyl (C=S) transfer to amines yields isothiocyanates in excellent yields;[5a–d] however, its toxicity and intolerance towards other sensitive functional groups limits its use. Thus, various C=S transfer reagents have been found to be ideal replacements for thiophosgene to access isothiocyanates.[5e–h] Isothiocyanates are also accessed by the addition of carbon disulfide (CS_2) to amines in the presence of a base to form dithiocarbamate salts, which on *in situ* desulfurization lead to the formation of isothiocyanates. Till date, various desulfurizing agents for dithiocarbamate have been reported in the literature.[6]

Synthesis of isothiocyanates from amines, however, faces few setbacks as most C=S transfer reagents are not readily available, and there is also the possibility of contamination by the formation of thioureas. In case of desulfurization of dithiocarbamate salts, electrophillic desulfurizing agents react with residual amines to hinder the reaction.

There are reports where isonitriles are reacted with elemental sulfur *via* catalytic sulfuration to yield the corresponding isothiocyanates.[7a–d] Boyer and Ramakrishnan demonstrated sulfuration of isonitriles using elemental sulfur and aryl isothiocyanates.[7e] Furthermore, the synthesis of isothiocyanates was demonstrated using isocyanates,[8] nitrile oxides and hydroximoyl chlorides,[9] nitroalkanes,[10] aldoximes,[11] and alkenes and alkyl halides.[12] Burkett *et al.* demonstrated 'catch and release' strategies from polymer-bound thiobenzophenone[13a] and polymer-bound thiocarbonate[13b] to realize the synthesis of isothiocyanates.

The Staudinger reaction is the reaction of an azide with triphenylphosphine (PPh_3) to form iminophosphorane with the

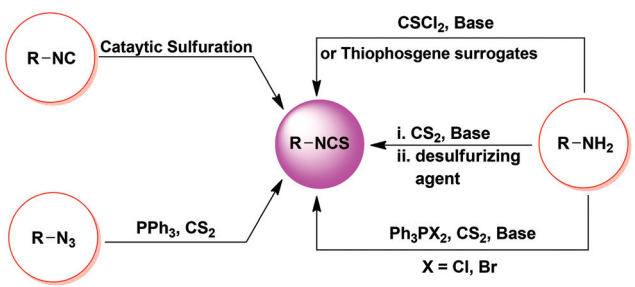

Fig. 1 Selected protocols for the synthesis of isothiocyanates.

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evolution of nitrogen gas.[14] These iminophosphoranes can be further used as intermediates to access a wide variety of nitrogen-containing organic compounds *via* the aza-Wittig reaction.[15] As a result, the Staudinger/aza-Wittig reaction was exploited soon after its discovery.[16] One such application is the synthesis of isothiocyanates from the reaction of iminophosphorane with CS_2, and this is well established as considerable amount of reports are available for the same.[16d–h] It is noteworthy that azaylides are also prepared by the reaction of triphenylphosphinedihalides with amines.[17]

The realm of peptidomimetics is rapidly advancing owing to the easy access and application of amino acid-derived precursors.[18] Likewise, amino acid-derived isothiocyanates are deemed necessary precursors for various peptidomimetic achievements; they are employed to access thiourea-,[19] selenourea-,[20a] guanidine and carbodiimide-[20b] and oxadiazole-tethered peptidomimetics.[20c]

Most commonly, the isothiocyanato group can be inserted into amino acid at the N-terminal (α-isothiocyanato alkyl esters, Fig. 2a) or C-terminal (N^{β}-protected amino alkyl isothiocyanates, Fig. 2b). Despite the importance of amino acid derived isothiocyanates, literature records regarding their synthesis are limited. This is understandable as the generalization of most aforementioned reagents to amino acid chemistry fails, and the availability of amino acid-derived precursors for isothiocyanates is limited. Furthermore, undesired reactivities of sensitive groups, steric factors of side chains and possible racemization are the major concerns while synthesizing amino acid-derived isothiocyanates.

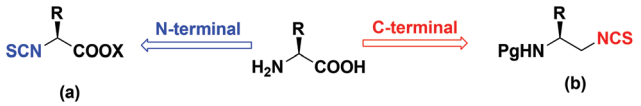
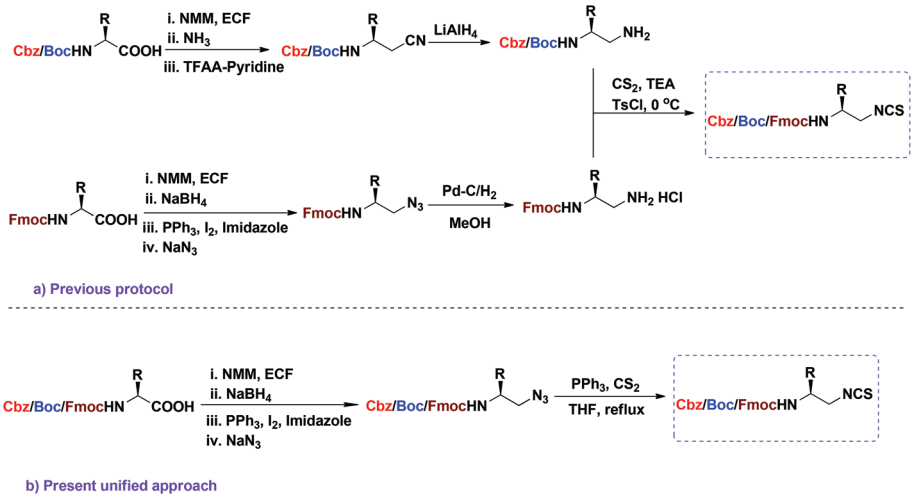


Fig. 2 (a) α-Isothiocyanato alkyl esters and (b) N^{β}-protected amino alkyl isothiocyanates.

A few reports are available on α-isothiocyanato alkyl esters, and they involve thiocarbonylation of α-amino alkyl esters by thiophosgene[5b–d,21a,b] and desulfurization of dithiocarbamate salts.[6b,20,21c–e]

Interestingly, protocols for N^{β}-protected amino alkyl isothiocyanates are very scant in the literature. In fact, the only available report to access these compounds was provided by our laboratory.[19] Isothiocyanates were prepared by the dithiocarbamate pathway from the corresponding amines by employing tosyl chloride (TsCl) as the desulfurizing agent. N^{β}-Fmoc-amino alkylamines were obtained by the reduction of the corresponding azides using Pd–C/H_2. On the other hand, N^{β}-Boc/Cbz-amino alkylamines were obtained by the reduction of the corresponding α-aminonitriles using lithium aluminium hydride ($LiAlH_4$). Hence, our previous protocol to access N^{β}-protected amino alkyl isothiocyanates employed two different routes while employing water sensitive $LiAlH_4$ and expensive Pd–C catalyst. Furthermore, the syntheses of N^{β}-Boc/Cbz-amino alkyl isothiocyanates and N^{β}-Fmoc-amino alkyl isothiocyanates from the corresponding N^{α}-protected amino acids were 5- and 6-step procedures, respectively (Scheme 1a). Recently, Bag and De demonstrated the synthesis of side-chain isothiocyanyl amino acid derivatives by employing a similar protocol.[22] Therein, isothiocyanates were obtained after converting azides to amines, which emphasized the necessity of using amines.

The dearth of literature regarding accessing N^{β}-protected amino alkyl isothiocyanates drove us to adopt an *ad hoc* approach. It was found that the Staudinger/aza-Wittig reaction was successfully employed to obtain sugar isothiocyanates from sugar azides.[16f] However, the application of the reaction for obtaining amino acid-derived isothiocyanates is yet to be explored. Furthermore, the type of protocol to be employed depends on the availability of precursors; luckily, N^{β}-Boc/Cbz/Fmoc-protected alkyl azides were accessed easily by employing reported protocols, where N^{α}-protected amino acids were con-

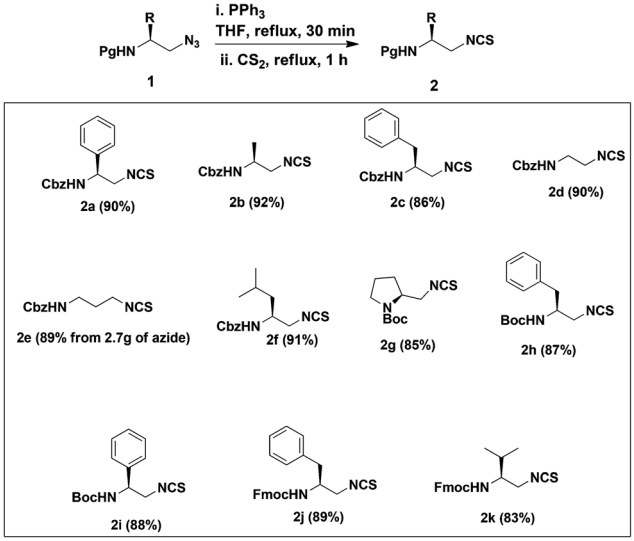


Scheme 1 Enantiopure synthesis of N^{β}-protected amino alkyl isothiocyanates: (a) the only protocol reported employing two separate routes and (b) the present unified approach.

verted to N^{β}-protected amino alkyl iodides, which on azidolysis gave the corresponding azides.[19,23] Thus, N^{β}-protected amino alkyl isothiocyanates were prepared without the need for corresponding amines, thus making the present protocol step-economical. Thus, herein, we describe an improved and unified approach for accessing N^{β}-protected amino alkyl isothiocyanates *via* the Staudinger/aza-Wittig reaction (Scheme 1b).

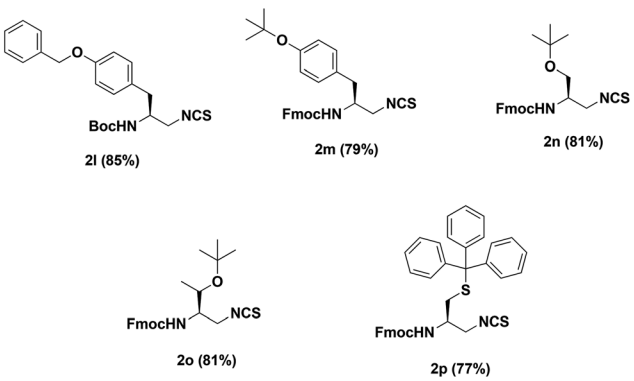
In a typical experiment, to a solution of Cbz-Phg-ψ[CH_2N_3] (**1a**, 1.0 mmol) in dry THF, PPh_3 (1.1 mmol) was added, and the solution was stirred at rt for 4 h. The progress of the entire reaction was monitored by thin layer chromatography (TLC). After consumption of the azide, CS_2 (10.0 mmol) was added and stirred at rt for 8 h to afford the corresponding isothiocyanate Cbz-Phg-ψ[CH_2NCS] (**2a**) in 91% yield after column purification. Excess CS_2 was used to ensure that the reaction did not suffer from the formation of the corresponding symmetrical carbodiimide, and THF was chosen as the solvent as it was found that various N^{β}-protected amino alkyl azides were completely soluble in it. As we were concerned about the prolonged reaction durations, we repeated the experiment under reflux condition. It was found that 1a completely reacted with PPh_3 to form iminophosphorane within 30 min. The reflux was continued after the addition of CS_2, and it was found to be highly effective as the corresponding isothiocyanate formation was completed in an hour to afford 90% yield. Therefore, the reflux condition was preferred for further preparation of N^{β}-protected alkyl isothiocyanates. Though the reactions in dichloromethane (DCM) and 1,4-dioxane were tested and found as productive as that in THF, the low boiling point of DCM deterred us from its further use in reflux conditions; on the other hand, due to its high boiling point, it was difficult to remove 1,4-dioxane from the reaction mixture, especially during large-scale synthesis. Various N^{β}-protected alkyl azides were easily converted to the corresponding isothiocyanates to give good yields of the products (Scheme 2, entries **2a–k**). Fmoc, Boc and Cbz protecting groups showed absolute compatabilities with the present strategy as the reaction was carried out in neutral conditions. The sterically hindered proline showed facile formation of isothiocyanate from the corresponding azide (Scheme 2, entry **2g**). Compound **2e** was obtained from large-scale synthesis (2.7 g, 11.5 mmol of azide), and the yield was found to be equally productive as that at small-scale. The purification of isothiocyanates was easy as they were relatively non-polar compared to triphenylphosphine disulfide, as the presence of triphenylphosphine disulfide resulted in difficulties during column purifications. To demonstrate the proficiency of the protocol, few N^{β}-protected alkyl azides with side chain protections were studied, and good yields of the products were obtained without affecting the side chain protections. Tertiary butyl and benzyl groups in the side chains were not affected at all (Table 1, entries **2l–o**).

It is important to note that the reaction was not inhibited by the presence of a side chain as bulky as in compound **2p**. The compatibilities of these compounds towards the present strategy were reflected in the isolated yields (Table 1, entries



Scheme 2 Synthesis of N^{β}-protected amino alkyl isothiocyanates from N^{β}-protected amino alkyl azides.

Table 1 Few side chain protected N^{β}-protected amino alkyl isothiocyanates



2l–p). During the process, we also prepared few hitherto unreported compounds (Scheme 2, entry **2g** and Table 1, entries **2l–p**), and all final compounds were completely characterized by IR, mass, melting point, optical rotation, and ^{1}H and ^{13}C NMR studies. The synthesized compounds were subjected to RP-HPLC analysis, and good purity was observed.

The syntheses of N^{β}-protected alkyl isothiocyanates from the corresponding azides were carried out in neutral conditions. Racemization studies were carried out to confirm the validity of the protocol, during which compound **2a** was coupled with (*R*)-1-phenylethylamine and (*S*)-1-phenylethylamine separately to obtain the corresponding compounds **3a** and **3a*** (Fig. 3). RP-HPLC analyses showed a retention time (t_R) of 14.28 min for **3a**, whereas the t_R value of **3a*** was 12.67 min.

Moreover, equimolar mixtures of **3a** and **3a*** showed retention times of 14.86 min and 12.79 min, respectively. Furthermore, ^{1}H NMR spectra of **3a** and **3a*** showed doublets

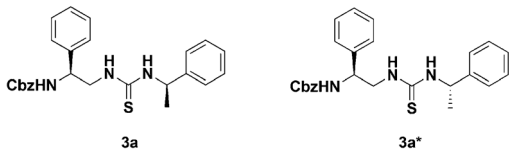


Fig. 3 Epimeric thiourea derivatives.

at δ 1.46 and 1.42, respectively, which corresponded to the methyl protons of each epimer. These analyses provided unequivocal evidence for racemization-free synthesis of the title compounds.

Conclusions

The Staudinger/aza-Wittig reaction was employed as an *ad hoc* approach for obtaining N^{β}-protected alkyl isothiocyanates from their corresponding azides. The protocol was an improved and unified version of our previous protocol for achieving the same products. It shall be the preferred choice considering that the precursor azides were easily accessible and most importantly, it eliminated the need for the use of amines to obtain isothiocyanates, due to which the protocol is step-economical and cost-effective. The neutral reaction condition benefitted the achievement of racemization-free synthesis of the title compounds bearing acid- and base-sensitive moieties.

Experimental section

General experimental details

All chemicals were used as obtained from Sigma Aldrich Company, USA. All solvents were dried and purified using procedures recommended in the literature whenever necessary. High-resolution mass spectra were recorded on a Micromass Q-TOF spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AV NMR 400 MHz and 100 MHz spectrometers, respectively. The RP-HPLC analysis of epimers was carried out using an Agilent instrument (method: gradient 0.1% TFA water-acetonitrile (0–100%) in 30 min; VWD at λ = 254 nm; flow rate: 1.0 mL min^{-1}; column: Agilent Eclipse, XDB-C18, pore size 5 μm, diameter × length = 4.6 × 150 nm). Optical rotations of the compounds were recorded at 25 °C; melting points were determined in an open capillary and were uncorrected. TLC experiments were performed using MERCK TLC aluminum sheets (silica gel 60 F254), and chromatograms were visualized with exposure to an iodine chamber, UV-lamp or $KMnO_4$ stain. Column chromatography was performed on silica gel (100–200 mesh) using ethylacetate and hexane (obtained from Merck and distilled and dried prior to use) mixtures as eluents.

General procedure for the synthesis of N^{β}-protected amino alkyl azides from N^{α}-protected amino acid

To a solution of N^{α}-protected amino acid (1.0 equiv.) in THF at −15 °C, *N*-methylmorpholine (NMM, 1.0 equiv.) and ethyl-chloroformate (ECF, 1.0 equiv.) were added, and the solution was stirred at the same temperature for 15 min. The inorganic salts were filtered off, and the filtrate was treated with moist $NaBH_4$ (2.0 equiv.) for 30 min. Excess water was added and stirred for 15 min. THF was removed by vacuum evaporation, and the resultant solution was extracted with EtOAc and washed with 10% Na_2CO_3, 10% citric acid, and brine; it was then dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The resultant compound without prior purification was used in the next step.

In the next step, a solution of N^{β}-protected aminol (1.0 equiv.) in CH_2Cl_2 was added to a stirred mixture of PPh_3 (3.0 equiv.), imidazole (5.0 equiv.) and iodine (3.0 equiv.) in dry CH_2Cl_2. After 6 h, the reaction mixture was evaporated, and the crude product was subjected to flash chromatography using 10% ethyl acetate in hexane as eluent to afford the corresponding N^{β}-protected amino alkyl iodide.

Then, to the solution of N^{β}-protected amino alkyl iodide (1.0 equiv.) in DMF, sodium azide (1.5 equiv.) was added, and the solution was stirred for 6 h at rt. The corresponding amino alkyl azide **1** was obtained in good yield and purity after aqueous workup.

General procedure for the synthesis of N^{β}-protected alkyl isothiocyanates from N^{β}-protected alkyl azides (2a–p)

To a stirred solution of N^{β}-protected alkyl azide (1.0 equiv.) in dry THF, PPh_3 (1.1 equiv.) was added, and the solution was refluxed for 30 min. After the consumption of azide (by TLC), CS_2 (10.0 equiv.) was added and refluxed for another hour. The solvent was evaporated under reduced pressure, and the obtained residue was subjected to column chromatography to isolate the corresponding isothiocyanate in good yield.

General procedure for preparing thiourea derivatives (3a and 3a*)

To a stirred solution of **2a** (1.0 equiv.) in THF, (*R*)-1-phenylethylamine (or (*S*)-1-phenylethyamine, 1.1 equiv.) was added, and the solution was stirred for 2 h at rt. The solvent was vacuum-evaporated and diluted with EtOAc, washed with 5% citric acid (2 × 10 mL), water (2 × 10 ml) and brine (10 mL), and dried over Na_2SO_4. The worked-up compound solution was vacuum-evaporated to obtain **3a** (or **3a***) in good yield and purity.

Cbz-Phg-ψ[CH$_2$NCS] (2a). White solid (90% yield); m.p. 131–133 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) +12.0; IR (ν_{max} cm^{-1}): 2200, 2096, 1686; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25–7.41 (m, 10H), 5.33 (d, *J* = 8Hz, 1H), 5.13 (dd, *J* = 20 Hz, 12 Hz, 2H), 4.96–5.02 (br m, 1H), 3.82–3.92 (br m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.5, 137.5, 135.9, 133.7, 129.1, 128.6, 128.5, 128.2, 128.1, 126.4, 67.3, 54.9, 49.7; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}N_2O_2SNa$ $[M + Na]^+$ 335.0830, found: 335.0832.

Cbz-Ala-ψ[CH$_2$NCS] (2b). White solid (92% yield); m.p. 112–114 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −97.3; IR (ν_{max} cm^{-1}): 2204, 2092, 1686; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 5.07–5.15 (m, 2H), 4.83 (br s, 1H), 3.97 (br m, 1H), 3.72 (d, *J* = 12 Hz, 1H), 3.56 (dd, *J* = 12 Hz, 4 Hz, 1H), 1.27 (d, *J* = 8

Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.4, 136.1, 132.8, 128.6, 128.3, 128.1, 67.0, 50.1, 46.9, 17.9; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}N_2O_2SNa$ $[M + Na]^+$ 273.0674, found: 273.0677.

Cbz-Phe-ψ[CH$_2$NCS] (2c). White solid (86% yield); m.p. 126–128 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −22.6; IR (ν_{max} cm^{-1}): 2206, 2104, 1697; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18–7.36 (m, 10H), 5.10 (s, 2H), 4.93 (d, *J* = 8 Hz, 1H), 4.09 (br m, 1H), 3.68 (dd, *J* = 12 Hz, 4 Hz, 1H), 3.50 (dd, *J* = 16 Hz, 4 Hz, 1H), 2.95 (dd, *J* = 12 Hz, 8 Hz, 1H), 2.84 (dd, *J* = 16 Hz, 8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.4, 138.2, 136.0, 133.3, 129.1, 128.9, 128.6, 128.3, 128.1, 127.7, 67.1, 52.1, 47.3, 37.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_2O_2SNa$ $[M + Na]^+$ 349.0987, found: 349.0986.

Cbz-Gly-ψ[CH$_2$NCS] (2d). Oily liquid (90% yield) IR (ν_{max} cm^{-1}): 2195, 2101, 1696; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H); 5.21 (s, 1H), 5.12 (s, 2H), 3.65 (t, *J* = 8 Hz, 2H), 3.41–3.46 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.2, 136.1, 132.8, 128.6, 128.3, 128.2, 67.1, 45.3, 41.0; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{12}N_2O_2SNa$ $[M + Na]^+$ 259.0517, found: 259.0518.

Cbz-β-Ala-ψ[CH$_2$NCS] (2e). White solid (89% yield); m.p. 55–57 °C; IR (ν_{max} cm^{-1}): 2184, 2099, 1692; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26–7.39 (m, 5H), 5.10 (s, 2H), 4.90 (br s, 1H), 3.59 (t, *J* = 8 Hz, 2H), 3.30–3.34 (m, 2H), 1.90–1.93 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.4, 136.3, 132.3, 128.5, 128.2, 128.1, 66.9, 42.6, 38.2, 30.2; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}N_2O_2SNa$ $[M + Na]^+$ 273.0674, found: 273.0677.

Cbz-Leu-ψ[CH$_2$NCS] (2f). White solid (91% yield); m.p. 106–108 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −112.0; IR (ν_{max} cm^{-1}): 2172, 2103, 1694; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31–7.37 (m, 5H), 5.11 (s, 2H), 4.79 (d, *J* = 4 Hz, 1H), 3.88–3.94 (m, 1H), 3.74 (dd, *J* = 16 Hz, 4 Hz, 1H), 3.55 (dd, *J* = 16 Hz, 4 Hz, 1H), 1.62–1.72 (m, 1H), 1.37–1.46 (m, 2H), 0.94 (d, *J* = 8 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.6, 136.1, 132.6, 128.5, 128.2, 128.1, 67.0, 49.2, 40.9, 24.7, 22.8, 22.0; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}N_2O_2SNa$ $[M + Na]^+$ 315.1143, found: 315.1141.

Boc-Pro-ψ[CH$_2$NCS] (2g). Oily liquid (85% yield); $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −99.4; IR (ν_{max} cm^{-1}): 2189, 2081, 1687; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85–3.96 (br m, 2H), 3.60–3.64(m, 1H), 3.37–3.48 (br m, 2H), 2.06–2.13 (m, 1H), 1.83–1.92 (m, 3H), 1.47 (s, 9H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.1, 131.5, 79.9, 56.4, 47.9, 47.1, 28.4, 23.7; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{18}N_2O_2SNa$ $[M + Na]^+$ 265.0987, found: 265.0983.

Boc-Phe-ψ[CH$_2$NCS] (2h). White solid (87% yield); m.p. 106–108 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −39.3; IR (ν_{max} cm^{-1}): 2203, 2113, 1685; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5H), 4.67 (br s, 1H), 4.02 (br s, 1H), 3.65 (br d, *J* = 12 Hz, 1H), 3.48 (dd, *J* = 12 Hz, 8 Hz, 1H), 2.92 (br m, 1H), 2.81 (dd, *J* = 12 Hz, 8 Hz, 1H), 1.44 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.9, 136.3, 132.8, 129.1, 128.8, 127.0, 80.1, 51.5, 47.6, 37.9, 28.3; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}N_2O_2SNa$ $[M + Na]^+$ 315.1143, found: 315.1141.

Boc-Phg-ψ[CH$_2$NCS] (2i). White solid (88% yield); m.p. 90–92 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) +11.0; IR (ν_{max} cm^{-1}): 2209, 2093, 1681; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26–7.40 (m, 5H), 5.05 (d, *J* = 12 Hz, 1H), 4.93 (br s, 1H), 3.82–3.92 (m, 2H), 1.46 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.9, 138.0, 133.3, 129.0, 128.5, 126.5, 80.5, 55.6, 49.8, 28.3; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}N_2O_2SNa$ $[M + Na]^+$ 301.0987, found: 301.0988.

Fmoc-Phe-ψ[CH$_2$NCS] (2j). White solid (89% yield); m.p. 187–189 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −18.1; (ν_{max} cm^{-1}): 2164, 2097, 1687; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8 Hz, 2H), 7.54 (t, *J* = 8 Hz, 2H), 7.29–7.41 (m, 9H), 4.87 (d, *J* = 8 Hz, 1H), 4.39 (d, *J* = 8 Hz, 2H), 4.19 (t, *J* = 8 Hz, 1H), 4.04 (br s, 1H), 3.44 (br d, *J* = 8 Hz, 1H), 3.34 (br d, *J* = 8 Hz, 1H), 2.79–2.84 (br m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.6, 143.7, 141.3, 136.8, 129.2, 129.0, 128.9, 128.7, 127.7, 127.0, 126.8, 124.9, 119.9, 66.7, 53.1, 51.8, 47.2, 38.0; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}N_2O_2SNa$ $[M + Na]^+$ 437.1300, found: 437.1303.

Fmoc-Val-ψ[CH$_2$NCS] (2k). White solid (83% yield); m.p. 164–166 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −74.0; IR (ν_{max} cm^{-1}): 2196, 2011, 1684; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8 Hz, 2H), 7.40 (t, *J* = 8 Hz, 2H), 7.33 (t, *J* = 8 Hz, 2H), 4.83 (d, J = 8 Hz, 1H), 4.46 (d, *J* = 8 Hz, 2H), 4.24 (t, *J* = 8 Hz, 1H), 3.69–3.75 (m, 2H), 3.55–3.61 (m, 1H), 1.80–1.89 (m, 1H), 0.97 (t, *J* = 8 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.9, 143.7, 141.3, 132.5, 127.7, 127.1, 127.0, 125.0, 124.9, 120.0, 66.7, 56.5, 47.3, 29.4, 19.3, 18.6; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}N_2O_2SNa$ $[M + Na]^+$ 389.1300, found: 389.1301.

Boc-Tyr(Bzl)-ψ[CH$_2$NCS] (2l). White solid (85% yield); m.p. 79–81 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) +19.6; IR (ν_{max} cm^{-1}): 2202, 2089, 1691; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32–7.43 (m, 5H), 7.12 (d, *J* = 8 Hz, 2H), 6.93 (d, *J* = 8 Hz, 2H), 5.05 (s, 2H), 4.65 (br s, 1H), 3.96 (br s, 1H), 3.63 (d, *J* = 12 Hz, 1H), 3.47 (dd, *J* = 12 Hz, 8 Hz, 1H), 2.86 (d, *J* = 8 Hz, 1H), 2.74 (dd, *J* = 12 Hz, 8 Hz, 1H), 1.44 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.9, 154.9, 136.9, 132.7, 130.1, 128.5, 127.9, 127.4, 115.2, 80.1, 70.0, 51.6, 47.5, 37.0, 28.3; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{26}N_2O_3SNa$ $[M + Na]^+$ 421.1562, found: 421.1566.

Fmoc-Tyr(^{t}Bu)-ψ[CH$_2$NCS] (2m). Gummy solid (79% yield); $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) +6.2; IR (ν_{max} cm^{-1}): 2186, 2096, 1701; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.83–7.76 (m, 12H), 4.91 (s, 1H), 4.42 (d, *J* = 8 Hz, 2H), 4.22 (t, *J* = 8 Hz, 1H), 4.02–4.10 (br m, 1H), 3.67 (br d, *J* = 12 Hz, 1H), 3.48 (br d, *J* = 12 Hz, 1H), 2.74–2.88 (br m, 2H), 1.33 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.4, 154.5, 143.6, 141.3, 133.2, 129.5, 128.5, 127.7, 127.1, 124.9, 124.4, 120.0, 78.5, 66.8, 52.1, 47.4, 47.2, 37.0, 28.8; HRMS (ESI): *m*/*z* calcd for $C_{29}H_{30}N_2O_3SNa$ $[M + Na]^+$ 509.1875, found: 509.1873.

Fmoc-Ser(^{t}Bu)-ψ[CH$_2$NCS] (2n). White solid (81% yield); m.p. 86–88 °C; $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) −14.3; IR: (ν_{max} cm^{-1}): 2119, 2074, 1691; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 2H), 7.59 (d, *J* = 8 Hz, 2H), 7.41 (t, *J* = 8 Hz, 2H), 7.32 (t, *J* = 8 Hz, 2H), 5.15 (d, *J* = 8 Hz, 1H), 4.41 (d, *J* = 8 Hz, 2H), 4.24 (t, *J* = 8 Hz, 1H), 3.99 (br s, 1H), 3.65 (br s, 2H), 3.54 (d, *J* = 8 Hz, 1H), 3.41–3.44 (m, 1H), 1.20 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.7, 143.8, 141.3, 132.2, 127.7, 127.1, 125.0, 124.9, 120.0, 73.6, 66.9, 59.9, 50.7, 47.2, 45.4, 27.4; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{26}N_2O_3SNa$ $[M + Na]^+$ 433.1562, found: 433.1560.

Fmoc-Thr(^{t}Bu)-ψ[CH$_2$NCS] (2o). Oily liquid (81% yield); $[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$) +9.7; IR (ν_{max} cm^{-1}): 2194, 2092, 1719; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 4 Hz, 2H), 7.60 (d, *J* = 8 Hz,

2H), 7.30–7.40 (m, 4H), 5.14 (d, J = 8 Hz, 1H), 4.44 (d, J = 8 Hz, 2H), 4.25 (t, J = 8 Hz, 1H), 3.87 (br d, J = 4 Hz, 1H), 3.70–3.80 (br m, 1H), 3.54–3.58 (m, 2H), 1.22 (t, J = 16 Hz, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.1, 143.8, 141.3, 131.8, 127.7, 127.0, 125.0, 124.9, 119.9, 74.2, 66.9, 64.9, 55.9, 47.2, 45.7, 28.7, 20.3; HRMS (ESI): m/z calcd for $C_{24}H_{28}N_2O_3SNa$ $[M + Na]^+$ 447.1718, found: 447.1715.

Fmoc-Cys(Trt)-ψ[CH_2NCS] (2p). Oily liquid (83% yield); $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) −13.9; IR (ν_{max} cm^{-1}): 2193, 2091, 1701; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (t, J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 2H), 7.20–7.41 (m, 19H), 4.59 (br s, 1H), 4.40 (d, J = 8 Hz, 2H), 4.19 (t, J = 8 Hz, 1H), 3.52 (br s, 3H), 2.46 (br s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.3, 144.1, 143.6, 141.3, 133.1, 129.4, 128.1, 128.0, 127.7, 127.0, 124.9, 120.0, 67.4, 66.7, 50.2, 47.7, 47.1, 33.2; HRMS (ESI): m/z calcd for $C_{38}H_{32}N_2O_2S_2Na$ $[M + Na]^+$ 635.1803, found: 635.1807.

Cbz-Phg-ψ[$CH_2NHCSNH$]-(*R*)-(+)-1-phenylethylamine (3a). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.17–7.34 (m, 15H), 6.60 (br s, 1H), 6.10 (br s, 1H), 5.66 (br s, 1H), 5.06 (dd, J = 16 Hz, 8 Hz, 2H), 4.72–4.76 (br m, 2H), 4.0–4.08 (br m, 1H), 3.69 (br d, J = 8 Hz, 1H), 1.46 (d, J = 8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 181.6, 156.5, 141.9, 139.0, 136.2, 129.0, 128.5, 128.2 (2C), 128.1, 127.8, 126.4, 125.7, 67.0, 60.3, 56.0, 53.8, 29.7.

Cbz-Phg-ψ[$CH_2NHCSNH$]-(*S*)-(−)-1-phenylethylamine (3a*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19–7.27 (m, 15H), 6.57 (br s, 1H), 6.04 (br s, 1H), 5.72 (br s, 1H), 4.97 (s, 2H), 4.63 (br s, 2H), 3.82–3.86 (br m, 1H), 3.71–3.77 (br m, 1H), 1.42 (d, J = 4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 181.5, 156.7, 142.0, 138.8, 136.2, 129.0, 128.5, 128.1, 127.9, 127.8, 126.4, 125.8, 66.8, 55.2, 53.5, 50.4, 23.6.

Conflicts of interest

Authors declare no conflict of interest.

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